

**United States Patent** [19]

Chen et al.

[11] **Patent Number:** 5,512,549[45] **Date of Patent:** Apr. 30, 1996

[54] **GLUCAGON-LIKE INSULINOTROPIC PEPTIDE ANALOGS, COMPOSITIONS, AND METHODS OF USE**

[75] Inventors: **Victor J. Chen**, Indianapolis; **Richard D. DiMarchi**, Carmel; **David L. Smiley**, Greenfield; **Russell D. Stucky**; **Aidas V. Kriauciunas**, Indianapolis, all of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **324,960**

[22] Filed: **Oct. 18, 1994**

[51] Int. Cl.<sup>6</sup> ..... **A61K 38/00**; A61K 38/26;  
C07K 14/605

[52] U.S. Cl. .... **514/12**; 530/308; 530/324

[58] Field of Search ..... 530/308, 324;  
514/12

[56] **References Cited****U.S. PATENT DOCUMENTS**

5,070,188	12/1991	Njieha et al.	530/324
5,118,666	6/1992	Habener	514/12
5,120,712	6/1992	Habener	514/12

**FOREIGN PATENT DOCUMENTS**

0082731	12/1982	European Pat. Off.
0619322A2	2/1994	European Pat. Off.
WO87/06941	11/1987	WIPO
WO90/11296	10/1990	WIPO
WO91/11457	8/1991	WIPO
WO93/18786	9/1993	WIPO
WO93/25579	12/1993	WIPO

**OTHER PUBLICATIONS**

Ser. No. 08/164,277, Galloway, et al, filing date Dec. 9, 1993.

Kreymann, et. al., "Glucagon-Like Peptide 7-36 A Physiological Incretin In Man", *The Lancet*, vol. 2, pp. 1300-1303 (Dec. 5, 1987).

Holst, et. al., "Truncated glucagon-like peptide I, an insulin-releasing hormone from the distal gut", *FEBS Letters*, vol. 211, No. 2, pp. 169-174 (Jan. 1987).

Mojsov, et. al., "Insulinotropic: Glucagon-like Peptide I (7-37) Co.-encoded in the Glucagon Gene Is a Potent Stimulator of Insulin Release in the Perfused Rat Pancreas", *The American Society for Clinical Investigation, Inc.*, vol. 79, pp. 616-619 (Feb. 1987).

Goke, et. al., "Glucagon like peptide-1 (7-36) amide is a new incretin/enterogastrone candidate", *European Journal of Clinical Investigation*, vol. 21, pp. 135-144 (1991).

Suzuki, et. al., "Effects Of GLP-1 And Its Fragment Peptides On Pancreatic Hormone Release", *Diabetes Research and Clinical Practice*, Supp. 1, vol. 5, ORA-007-007, p. S30 (1988).

Weir, et. al., "Glucagonlike Peptide I (7-37) Actions on Endocrine Pancreas", *Diabetes*, vol. 38, pp. 338-342 (Mar. 1989).

Komatsu, et. al., "Glucagonostatic and Insulinotropic Action of Glucagonlike Peptide I-(7-36)-Amide", *Diabetes*, vol. 38, pp. 903-905, (Jul. 1989).

Orskov, et. al., "Complete Sequences of Glucagon-like Peptide-1 from Human and Pig Small Intestine", *The Journal of Biological Chemistry*, vol. 264, No. 22, pp. 12826-12929, (Aug. 5, 1989).

Takahashi, et. al., "Radioimmunoassay For Glucagon-Like Peptide-1 In Human Plasma Using N-Terminal And C-Terminal Directed Antibodies: A Physiologic Insulinotropic Role of GLP-1 (7-36 Amide)", *Biomedical Research* vol. 11 (2), pp. 99-108, (1990).

Mojsov, "Structural requirements for biological activity of glucagon-like peptide-I", *Int J Peptide Protein Res*, vol. 40, pp. 333-343 (1992).

Orskov, "Glucagon-like peptide-1, a new hormone of the entero-insular axis", *Diabetologia*, vol. 35, pp. 701-711 (1992).

Thorens, et. al., "Glucagon-Like Peptide-I and the Control of Insulin Secretion in the Normal State and in NIDDM", *Diabetes*, vol. 42, pp. 1219-1225 (Sep. 1992).

Nauck, et. al., "Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide in Type 2 (non-insulin-dependent) diabetic patients", *Diabetologia*, vol. 36, pp. 741-744 (1993).

Nauck, et. al., "Preserved Incretin Activity of Glucagon-like Peptide 1 (7-36 Amide) but Not of Synthetic Human Gastric Inhibitory Polypeptide in Patients with Type-2 Diabetes Mellitus", *The American Society for Clinical Investigation, Inc.*, vol. 91, pp. 301-307, (Jan. 1993).

Hvidberg, et. al., "Effect of Glucagon-like Peptide-1 (proglucagon 78-107 amide) on Hepatic Glucose Production in Healthy Man", *Metabolism*, vol. 43, No. 1, pp. 104-108, (Jan. 1994).

Fehmann, et al, "Insulinotropic Glucagonlike Peptide-I (7-37) (7-36) Amide A New Incretin Hormone", *TEM*, vol. 3, No. 5, 158-163, (1992).

Hashimoto, et al, "Synthesis of Palmitoyl Derivatives of Insulin and Their Biological Activities", *Pharmaceutical Research*, vol. 6, No. 2, 171-176 (1989).

Suzuki, S., et al. "Comparison of the Effects of Various C-Terminal and N-Terminal Fragment Peptides of Glucagon-Like Peptide-1 on Insulin and Glucagon Release from the Isolated Perfused Rat Pancreas" *Endocrinology*, vol. 125, No. 6, 3109-3114 (1989).

*Primary Examiner*—Jill Warden

*Assistant Examiner*—Benet Prickril

*Attorney, Agent, or Firm*—Ronald S. Maciak; David E. Boone

[57] **ABSTRACT**

Glucagon-like insulinotropic peptide (GLP-1(7-37)) analogs and derivatives are disclosed. The analogs include amino acid substitutions, amino and carboxyl terminal modifications, and C<sub>6</sub>-C<sub>10</sub> acylations. The claimed compounds stimulate the secretion or biosynthesis of insulin in poorly functioning beta cells and are therefore useful in treating Type II diabetics

**28 Claims, No Drawings**

# GLUCAGON-LIKE INSULINOTROPIC PEPTIDE ANALOGS, COMPOSITIONS, AND METHODS OF USE

## FIELD OF INVENTION

The present invention relates to organic and peptide chemistry as applied to pharmaceutical research and development. The invention provides novel peptide derivatives and compositions that are useful for up-regulating insulin expression in mammals and for treating diabetes.

## BACKGROUND OF THE INVENTION

Endocrine secretions of pancreatic islets are regulated by complex control mechanisms driven not only by blood-borne metabolites such as glucose, amino acids, and catecholamines, but also by local paracrine influences. The major pancreatic islet hormones, glucagon, insulin and somatostatin, interact with specific pancreatic cell types (A, B, and D cells, respectively) to modulate the secretory response. Although insulin secretion is predominantly controlled by blood glucose levels, somatostatin inhibits glucose-mediated insulin secretion. In addition to inter-islet paracrine regulation of insulin secretion, there is evidence to support the existence of insulinotropic factors in the intestine. This concept originates from observations that glucose taken orally is a much more potent stimulant of insulin secretion than is a comparable amount of glucose given intravenously.

The human hormone glucagon is a 29-amino acid hormone produced in pancreatic A-cells. The hormone belongs to a multigene family of structurally related peptides that include secretin, gastric inhibitory peptide, vasoactive intestinal peptide and glicentin. These peptides variously regulate carbohydrate metabolism, gastrointestinal mobility and secretory processing. However, the principal recognized actions of pancreatic glucagon are to promote hepatic glycogenolysis and glyconeogenesis, resulting in an elevation of blood sugar levels. In this regard, the actions of glucagon are counter regulatory to those of insulin and may contribute to the hyperglycemia that accompanies Diabetes mellitus (Lund, P. K., et al., *Proc. Natl. Acad. Sci. U.S.A.*, 79:345-349 (1982)).

When glucagon binds to its receptor on insulin producing cells, cAMP production increases which in turn stimulates insulin expression (Korman, L. Y., et al., *Diabetes*, 34:717-722 (1985)). Moreover, high levels of insulin down-regulate glucagon synthesis by a feedback inhibition mechanism (Ganong, W. F., *Review of Medical Physiology*, Lange Publications, Los Altos, Calif., p. 273 (1979)). Thus, the expression of glucagon is carefully regulated by insulin, and ultimately by serum glucose levels.

Proglucagon, the precursor form of glucagon, is encoded by a 360 base pair gene and is processed to form proglucagon (Lund, et al., *Proc. Natl. Acad. Sci. U.S.A.* 79:345-349 (1982)). Patzelt, et al. (*Nature*, 282:260-266 (1979)) demonstrated that proglucagon is further processed into glucagon and a second peptide. Later experiments demonstrated that proglucagon is cleaved carboxyl to Lys-Arg or Arg-Arg residues (Lund, P. K., et al., Lopez L. C., et al., *Proc. Natl. Acad. Sci. U.S.A.*, 80:5485-5489 (1983), and Bell, G. I., et al., *Nature* 302:716-718 (1983)). Bell, G. I., et al., also discovered that proglucagon contained three discrete and highly homologous peptide regions which were designated glucagon, glucagon-like peptide 1 (GLP-1), and glucagon-like peptide 2 (GLP-2). Lopez, et al., demon-

strated that GLP-1 was a 37 amino acid peptide and that GLP-2 was a 34 amino acid peptide. Analogous studies on the structure of rat preproglucagon revealed a similar pattern of proteolytic cleavage at Lys-Arg or Arg-Arg residues, resulting in the formation of glucagon, GLP-1, and GLP-2 (Heinrich, G., et al., *Endocrinol.*, 115:2176-2181 (1984)). Finally, human, rat, bovine, and hamster sequences of GLP-1 have been found to be identical (Ghiglione, M., et al., *Diabetologia*, 27:599-600 (1984)).

The conclusion reached by Lopez, et al., regarding the size of GLP-1 was confirmed by studying the molecular forms of GLP-1 found in the human pancreas (Uttenthal, L. O., et al. *J. Clin. Endocrinol. Metabol.*, 61:472-479 (1985)). Their research showed that GLP-1 and GLP-2 are present in the pancreas as 37 and 34 amino acid peptides respectively.

The similarity between GLP-1 and glucagon suggested to early investigators that GLP-1 might have biological activity. Although some investigators found that GLP-1 could induce rat brain cells to synthesize cAMP (Hoosein, N. M., et al., *Febs Lett.* 178:83-86 (1984)), other investigators failed to identify any physiological role for GLP-1 (Lopez, L. C., et al. supra). The failure to identify any physiological role for GLP-1 caused some investigators to question whether GLP-1 was in fact a hormone and whether the relatedness between glucagon and GLP-1 might be artifactual.

It has now been shown that biologically processed forms of GLP-1 have insulinotropic properties and may delay gastric emptying. GLP-1(7-34) and GLP-1(7-35) are disclosed in U.S. Pat. No. 5,118,666, herein incorporated by reference. GLP-1(7-37) is disclosed in U.S. Pat. No. 5,120,712, herein incorporated by reference.

Variants and analogs of GLP-1 are known in the art. These variants and analogs include, for example, GLP-1(7-36), Gln<sup>9</sup>-GLP-1(7-37), D-Gln<sup>9</sup>-GLP-1(7-37), acetyl-Lys<sup>9</sup>-GLP-1(7-37), Thr<sup>16</sup>-Lys<sup>18</sup>-GLP-1(7-37), and Lys<sup>18</sup>-GLP-1(7-37). Derivatives of GLP-1 include, for example, acid addition salts, carboxylate salts, lower alkyl esters, and amides (see, e.g., WO91/11457). Generally, the various disclosed forms of GLP-1 are known to stimulate insulin secretion (insulinotropic action) and cAMP formation (see, e.g., Mojsov, S., *Int. J. Peptide Protein Research*, 40:333-343 (1992)).

More importantly, numerous investigators have demonstrated a predictable relationship between various in vitro laboratory experiments and mammalian, especially human, insulinotropic responses to exogenous administration of GLP-1, GLP-1(7-36) amide, and GLP-1(7-37) acid (see, e.g., Nauck, M. A., et al., *Diabetologia*, 36:741-744 (1993); Gutniak, M., et al., *New England J. of Medicine*, 326(20):1316-1322 (1992); Nauck, M. A., et al., *J. Clin. Invest.*, 91:301-307 (1993); and Thorens, B., et al., *Diabetes*, 42:1219-1225 (1993)).

The fundamental defects responsible for causing hyperglycemia in mature onset diabetes include impaired secretion of endogenous insulin and resistance to the effects of insulin by muscle and liver tissue (Galloway, J. S., *Diabetes Care*, 13:1209-1239, (1990)). The latter defect results in excess glucose production in the liver. Thus, whereas a normal individual releases glucose at the rate of approximately 2 mg/kg/minute, a patient with mature onset diabetes releases glucose at a rate exceeding 2.5 mg/kg/minute, resulting in a net excess of at least 70 grams of glucose per 24 hours.

Because there exists exceedingly high correlations between hepatic glucose production, fasting blood glucose



the protein portion of Formula 1 can be obtained. Although it may be produced by solid phase peptide synthesis or recombinant methods, recombinant methods may be preferable because higher yields are possible. The basic steps in recombinant production are:

- a) isolating a natural DNA sequence encoding GLP-1 or constructing a synthetic or semi-synthetic DNA coding sequence for GLP-1,
- b) placing the coding sequence into an expression vector in a manner suitable for expressing proteins either alone or as a fusion proteins,
- c) transforming an appropriate eukaryotic or prokaryotic host cell with the expression vector,
- d) culturing the transformed host cell under conditions that will permit expression of a GLP-1 intermediate, and
- e) recovering and purifying the recombinantly produced protein.

As previously stated, the coding sequences may be wholly synthetic or the result of modifications to the larger, native glucagon-encoding DNA. A DNA sequence that encodes preproglucagon is presented in Lund, et al., *Proc. Natl. Acad. Sci. U.S.A.* 79:345-349 (1982) and may be used as starting material in the semisynthetic production of the compounds of the present invention by altering the native sequence to achieve the desired results.

Synthetic genes, the in vitro or in vivo transcription and translation of which results in the production of the protein portion of Formula 1, may be constructed by techniques well known in the art. Owing to the natural degeneracy of the genetic code, the skilled artisan will recognize that a sizable yet definite number of DNA sequences may be constructed, all of which encode the polypeptide of Formula 1.

The methodology of synthetic gene construction is well known in the art. See Brown, et al. (1979) *Methods in Enzymology*, Academic Press, N.Y., Vol. 68, pgs. 109-151. DNA sequences that encode the protein backbone of Formula 1 can be designed based on the amino acid sequences herein disclosed. Once designed, the sequence itself may be generated using conventional DNA synthesizing apparatus such as the Model 380A or 380B DNA synthesizers (PE-Applied Biosystems, Inc., 850 Lincoln Center Drive, Foster City, Calif. 94404).

To effect expression of the polypeptide of Formula 1, one inserts the engineered synthetic DNA sequence in any one of many appropriate recombinant DNA expression vectors through the use of appropriate restriction endonucleases. See generally Maniatis et al. (1989) *Molecular Cloning; A Laboratory Manual*, Cold Springs Harbor Laboratory Press, N.Y., Vol. 1-3. Restriction endonuclease cleavage sites are engineered into either end of the GLP-1 intermediate-encoding DNA to facilitate isolation from, and integration into, known amplification and expression vectors. The particular endonucleases employed will be dictated by the restriction endonuclease cleavage pattern of the parent expression vector to be employed. The choice of restriction sites are chosen so as to properly orient the coding sequence with control sequences to achieve proper in-frame reading and expression of the protein of interest. The coding sequence must be positioned so as to be in proper reading frame with the promoter and ribosome binding site of the expression vector, both of which are functional in the host cell in which the protein is to be expressed.

To achieve efficient transcription of the synthetic gene, it must be operably associated with a promoter-operator region. Therefore, the promoter-operator region of the syn-

thetic gene is placed in the same sequential orientation with respect to the ATG start codon of the synthetic gene.

A variety of expression vectors useful for transforming prokaryotic and eukaryotic cells are well known in the art. See *The Promega Biological Research Products Catalogue* (1992) (Promega Corp., 2800 Woods Hollow Road, Madison, Wis., 53711-5399); and *The Stratagene Cloning Systems Catalogue* (1992) (Stratagene Corp., 11011 North Torrey Pines Road, La Jolla, Calif., 92037). Also, U.S. Pat. No. 4,710,473 describes circular DNA plasmid transformation vectors useful for expression of exogenous genes in *E. coli* at high levels. These plasmids are useful as transformation vectors in recombinant DNA procedures and

- (a) confer on the plasmid the capacity for autonomous replication in a host cell;
- (b) control autonomous plasmid replication in relation to the temperature at which host cell cultures are maintained;
- (c) stabilize maintenance of the plasmid in host cell populations;
- (d) direct synthesis of a protein prod. indicative of plasmid maintenance in a host cell population;
- (e) provide in series restriction endonuclease recognition sites unique to the plasmid; and
- (f) terminate mRNA transcription.

These circular DNA plasmids are useful as vectors in recombinant DNA procedures for securing high levels of expression of exogenous genes.

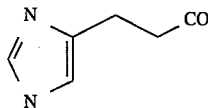
Having constructed an expression vector for the protein of Formula 1, the next step is to place the vector into a suitable cell and thereby construct a recombinant host cell useful for expressing the polypeptide. Techniques for transforming cells with recombinant DNA vectors are well known in the art and may be found in such general references as Maniatis, et al. supra. Host cells made be constructed from either eukaryotic or prokaryotic cells.

Prokaryotic host cells generally produce the protein at higher rates and are easier to culture. Proteins which are expressed in high-level bacterial expression systems characteristically aggregate in granules or inclusion bodies which contain high levels of the overexpressed protein. Such protein aggregates typically must be solubilized, denatured and refolded using techniques well known in the art. See Kreuger, et al. (1990) in *Protein Folding*, Gierasch and King, eds., pgs 136-142, American Association for the Advancement of Science Publication No. 89-18S, Washington, D.C.; and U.S. Pat. No. 4,923,967.

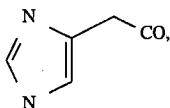
Having preparing the polypeptide backbone of Formula 1, an imidazole, as defined above in the "Summary of the Invention," is added to the amino terminus to produce various embodiments of the present invention. Coupling the imidazolic group to the polypeptide of Formula 1 is accomplished by synthetic chemical means. Because all of the various organic groups contemplated in this invention contain a carboxylic acid, the imidazolic group can be added by solid phase protein synthesis analogous to adding an amino acid to the N-terminus of a polypeptide. Alternatively, an activated ester of the imidazolic group can be added by standard chemical reaction methods.

7

Preferred imidazolic groups of the present invention are:

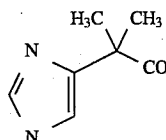


4-imidazopropionyl (des-amino-histidyl)  
4-imidazoacetyl



and

4-imidazo- $\alpha,\alpha$ dimethyl-acetyl



The most preferred group is 4-imidazopropionyl.

Further embodiments of the present invention are made by acylating the epsilon amino group of the Lys<sup>34</sup> residue. Straight chain acyl additions containing between 6 to 10 carbon atoms are preferred and unbranched C<sub>8</sub> is most preferred.

Other embodiment of the present invention include amino acid substitutions at position 26 (Xaa) of Formula 1. Lys, and Arg are acceptable at this position, though Arg is preferred.

Modifications at the carboxy terminus are also included in the present invention. As such R<sup>3</sup> may be Gly-OH or NH<sub>2</sub>; Gly-OH is preferred over the carboxy terminal amide embodiments.

Addition of an acyl group to the epsilon amino group of Lys<sup>34</sup> may be accomplished using any one of a variety of methods known in the art. See *Bioconjugate Chem.* "Chemical Modifications of Proteins: History and Applications" pages 1, 2-12 (1990); Hashimoto et al., *Pharmaceutical Res.* "Synthesis of Palmitoyl Derivatives of Insulin and their Biological Activity" Vol. 6, No: 2 pp.171-176 (1989).

For example, the N-hydroxy-succinimide ester of octanoic acid can be added to the lysyl-epsilon amine using 50% acetonitrile in borate buffer. The peptide can be acylated either before or after the imidazolic group is added. Moreover, if the peptide is prepared recombinantly, acylation prior to enzymatic cleavage is possible.

The present invention also includes salt forms of GLP-1(7-37) analogs. Compounds of the invention may be sufficiently acidic or sufficiently basic to react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluene-sulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate,

8

oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylene-sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Preferred acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and, especially, hydrochloric acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like. Salt forms of GLP-1(7-37) analogs are particularly preferred. When the compounds of the invention are used for therapeutic purposes, those compounds may also be in the form of a salt, but the salt must be pharmaceutically acceptable.

GLP-1(7-37) analogs of the present invention demonstrate insulinotropic activity. The term "insulinotropic activity" relates to the ability of a substance to stimulate, or cause the stimulation of, the synthesis or expression of the hormone insulin.

The insulinotropic property of a compound may be determined by providing that compound to animal cells, or injecting that compound into animals and monitoring the release of immunoreactive insulin (IRI) into the media or circulatory system of the animal, respectively. The presence of IRI is detected through the use of a radioimmunoassay which can specifically detect insulin.

Although any radioimmunoassay capable of detecting the presence of IRI may be employed, a modification of the assay may also be used. See J. D. M., et al., *Acta Endocrinol.*, 70:487-509 (1972). The insulinotropic property of a compound may also be determined by pancreatic infusion. See Penhos, J. C., et al., *Diabetes*, 18:733-738 (1969).

The present invention also provides pharmaceutical compositions comprising a compound of the present invention in combination with a pharmaceutically acceptable carrier, diluent, or excipient. Such pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art, and are administered individually or in combination with other therapeutic agents, preferably via parenteral routes. An especially preferred route is by subcutaneous administration.

Parenteral dosages may range from about 1 pg/kg to about 1,000 μg/kg of body weight, although lower or higher dosages may be administered. The required dosage will depend upon the severity of the condition of the patient and upon such criteria as the patient's height, weight, sex, age, and medical history.

In making the compositions of the present invention, the active ingredient, which comprises at least one compound of the present invention, is usually mixed with an excipient or diluted by an excipient. When an excipient is used as a diluent, it may be a semi-solid or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Liquid excipients are preferred.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to particle size of less than about 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.